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EXAMINER
MYERS, CARLA J

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1634	28

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 08/976,560	Applicant(s) FREIMER ET AL.	
	Examiner Carla Myers	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 July 2002 and 21 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 25-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 25-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. This action is in response to the Appeal Brief filed July 26, 2002. This action contains new grounds of rejection and is made non-final.

2. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see, for example, page 18). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

3. Claims 1-12 and 25-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (i) methods of detecting an increased susceptibility to bipolar mood disorder (BP) wherein said methods comprise performing a pedigree analysis for the individual's family and analyzing the DNA from family members for linkage of markers on the short arm of chromosome 18 between and inclusive of SAVA5 and ga203, D18S1140 and ga203, SAVA5 and W3422, S18S1140 and W3422, D18S1140 and ta201 and S18S59 and ta201, and (ii) methods of detecting an increased susceptibility to bipolar mood disorder by assaying for the presence of a 154 bp allele at D18S59 or a 271 bp allele at D18S476 wherein the presence of either of said alleles is indicative of an increased susceptibility to BP, does not reasonably provide enablement for (a) a method of detecting an increased susceptibility to bipolar mood disorder in the general population by detecting any polymorphism between SAVA5 and ga203 wherein any polymorphism associated with BP indicates an increased susceptibility to develop BP or (b) a method for detecting the presence of any BP susceptibility DNA polymorphism wherein said method comprises detecting a polymorphism over-represented on disease chromosomes or typing blood relatives to detect the presence of a new polymorphism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The claims as broadly written include methods of detecting an increased susceptibility to bipolar mood disorder by detecting any DNA polymorphisms within a 300 kb or 500 kb region of chromosome 18 between and inclusive of the markers SAVA5 and ga203. In view of the teachings in the specification, it has been interpreted that the claims as broadly written include methods in which any type of genetic alteration is detected in the region of SAVA5 to ga203 as indicative of susceptibility to BP (see, for example, pages 12-13 of the specification). Accordingly, the claims include methods in which any substitution, addition, deletion, translocation or splice variant of a particular gene is detected as indicative of BP. The claims also include methods which identify novel polymorphisms that are associated with BP. However, the specification has not taught a representative number of polymorphisms within the SAVA5 to ga203 region that can be used to diagnose bipolar mood disorder within the general population. The claims as written are not commensurate in scope with the disclosure for the following reasons:

The specification teaches that markers within chromosome 18 were used to delineate a 500 kb and 300 kb subregion of chromosome 18p that is associated with bipolar mood disorder. Haplotype analysis was performed by assaying blood samples from affected and unaffected family members. Through this analysis, a region from SAVA5 to ga203 of chromosome 18 was

identified as being linked with bipolar susceptibility disorder. Accordingly, the specification teaches methods in which susceptibility to bipolar mood disorder can be determined by performing a pedigree analysis wherein said analysis detects the presence of a polymorphic marker between SAVA5 and ga203 of chromosome 18 in a test individual, wherein said polymorphic marker is known to be present in affected family members and is absent in unaffected family members. Furthermore, the specification teaches that a 154 bp allele of D18S59 and a 271 bp allele of D18S476 are each over-represented in individuals having BP, as compared to individuals in the general population. However, the claims as written include methods in which any polymorphism between SAVA5 to ga203 is detected in the general population as indicative of an increased susceptibility to BP. The teachings in the specification of 2 polymorphic markers (i.e., the 154 bp allele of D18S59 and the 271 bp allele of D18S476) is not representative of the claimed genus of any DNA polymorphism between SAVA5 to ga203 associated with BP. While the stated D18S59 and D18S476 markers can be used to analyze the general population for increased susceptibility to BP, the ability to use other, unidentified polymorphisms to diagnose BP is highly unpredictable. Additionally, the specification does not identify any particular single nucleotide polymorphisms that are associated with BP and does not teach any other type of genetic alterations that are associated with BP. As discussed in the specification, extensive experimentation is required to identify additional polymorphisms and other types of genetic alterations that are associated with BP. The specification (beginning at page 31) provides an outline of the research that can be performed to identify polymorphisms associated with BP. In particular, the specification teaches that a P1 clonal library can be made to identify candidate cDNAs which would then be sequenced and compared to nucleic acid

databases to identify a gene or genes which may constitute the bipolar susceptibility gene. The cDNAs identified that map to the minimal candidate region are then used as probes to screen the P1 phage contig library. This screening then identifies new microsatellite markers which are used to genotype the linkage disequilibrium sample. The cDNAs identified by these screens are then used to screen patient DNA for mutations and polymorphisms associated with bipolar disorders.

The art corroborates the unpredictability in identifying polymorphisms and mutations associated with BP and in identifying a specific loci within chromosome 18 that is definitively associated with BP. For example, McInnes teach that interpreting results form linkage analysis of bipolar mood disorder and other behavioral phenotypes is very difficult and often misleading because behavioral phenotypes are difficult to define, as they are etiologically heterogeneous and there is a lack of knowledge as to the mode of transmission of these diseases. McInnes concluded that it is unlikely that any one linkage study will yield sufficient evidence to localize a gene for any psychiatric disorder (page 13060, col. 2, paragraph 1). However, McInnes performed a genome screening analysis for possible genes associated with BP and found suggestive lod scores in segments 18q, 18p and 11p, including an marker D18S59 (see abstract and Table 1). McInnes state that the point of their study was to detect chromosomal regions which merit further investigation (page 13063, col. 1, paragraph 1) and McInnes specifically identified the telomere of 18p as a region that should be further studied (page 13064, col. 1). McInnes teaches that genome screening is the first step of a multi-step process for identifying genes for complex traits and that several additional steps and experiments would be required to delineate a clear candidate region (page 13064, col. 2). Easterling (1997) discloses a high resolution integrated map of 18p11.2, which is a 40 cM region believed to contain a potential bipolar susceptibility

locus (see Figure 1). However, even with these high resolution maps and linkage studies, no specific polymorphisms or individual loci were identified as the bipolar susceptibility locus as of 1999. Gerson (1998) reviewed the progress in identifying genes associated with manic-depressive illness and concluded that while chromosome 18, and particularly the short arm of chromosome 18, is one of the best candidate locations for a bipolar susceptibility gene, and that the positive linkage results represent important progress, scientists are still a long way from demonstrating a disease mutation correlated with bipolar illness (page 239, col. 2). Nothen (1999) concluded that as late as 1999 that the data in the art supports the hypothesis that a susceptibility locus exists and may specifically exist on chromosome 18, but does not provide a reasonable expectation that polymorphisms in the region of 18p are associated with a bipolar susceptibility locus or what that locus will be.

The teachings in the specification do not provide a reasonable expectation that one of skill in the art can identify polymorphisms associated with bipolar mood disorder or can identify a bipolar susceptibility locus without undue experimentation because of the high level of unpredictability in the art (as discussed above) and because the specification has not provided evidence that would allow the skilled artisan to predict the location and identity of additional bipolar susceptibility polymorphisms. The specification presents data defining a smaller region of the 18pter which has a higher probability of containing a susceptibility locus, but as of 1999, the art indicates that scientists are a long way from pinpointing specific polymorphisms and mutations that are associated with bipolar disease. The specification describes a research project for searching for polymorphisms that may exist in the defined region but the protocol described constitutes undue experimentation because the skilled artisan would be required to perform a

large amount of essentially random screening of the defined region and would not be able to reasonably predict from the specification the identity of the polymorphisms associated with BP. Furthermore, the claims as written are claims to a research project without a predictable outcome because they encompass methods which detect novel bipolar disease susceptibility polymorphisms. The art makes clear that this objective is of great interest and the target of extensive research by many groups. In fact, many groups have taken the same approach as described in the specification for identifying such a bipolar locus without success. The specification essentially suggests that the artisan should analyze all possible polymorphisms within the 500 kb region of SAVA5 to ga203 and then determine which polymorphisms within this region "work" (i.e., determine which polymorphisms within the broad genus of polymorphisms could be used to diagnose BP).

The fact that the specification presents evidence of linkage to the recited markers in a defined region of chromosome 18 is useful in analyzing family members by pedigree analysis for the inheritance of markers within this defined region. However, this finding does not allow one of skill in the art to screen the general population for any polymorphism between SAVA5 and ga203 for susceptibility to BP. The region between SAVA5 and ga203 is expected to contain numerous polymorphisms and mutations that are not associated with BP. Thereby, the detection of these variants in the general population would not be predictive of susceptibility to BP. Only specific polymorphisms and mutations within the defined region will be found to be correlated with BP. The specification does not provide sufficient guidance as to how to apply the claimed method of diagnosis to the general population by detecting the presence of any polymorphism between SAVA5 and ga203. As stated in *Vaek* (20 USPQ2d 1438), the "specification must

teach those of skill in the art how to make and how to use the invention as *broadly* as it is claimed" (emphasis added). The amount of guidance needed to enable the invention is related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher* 427 F. 2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Predictability or lack thereof in the art refers to the ability of one of skill in the art to extrapolate the disclosed or known results to the invention that is claimed. If one of skill in the art can readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is unpredictability in the art." With respect to the present invention, one cannot readily anticipate what additional polymorphisms may exist between SAVA5 and ga203 which are associated with BP and which could be used to screen any individual for susceptibility to BP. In view of the high level of unpredictability in the art and the lack of guidance provided in the specification, undue experimentation would be required for one of skill in the art to practice the invention as it is broadly claimed.

RESPONSE TO ARGUMENTS:

In the brief, it is argued that the disclosure is enabling for the full scope of the claimed invention because Applicants have described a number of polymorphisms associated with BP and have provided guidance as to how to identify additional polymorphisms. In particular, it is stated that polymorphisms have been identified which are associated with BP and that the polymorphisms were identified using both pedigree analysis and an analysis of unrelated individuals. This argument has been fully considered but is not persuasive because with respect

to unrelated individuals, the specification has established only that allele 154 at D18S59 and allele 271 at D18S476 are over-represented in populations having BP. These 2 alleles are not considered to be representative of the broadly claimed genus of any polymorphism on chromosome 18p between SAVA5 and ga203 associated with BP.

It is argued that the declaration of Alison McInnes submitted with the after-final amendment of October 10, 2001 establishes that the specification provides sufficient guidance to identify additional polymorphisms in the "narrow interval" of SAVA5 and ga203. This argument and the declaration of Alison McInnes have been fully considered but are not persuasive to overcome the present grounds of rejection. It is first noted that the claims are inclusive of identifying a polymorphism in a region that contains approximately 500kb and that this is in fact a large region of the genome to scan for the presence of polymorphisms associated with BP. Secondly, the declaration states that the references of Escamilla (1999 and 2001) provide further evidence of the association between BP and markers within the SAVA5 and ga203 interval. While it is noted that these references discuss an association between markers in this 18p region and BP, the references also emphasize the unpredictability in the art in identifying a particular loci associated with BP and the unpredictability in identifying particular polymorphisms associated with BP. Specifically, the Escamilla (2001, pages 212-213) reference, in which the present inventors are listed as co-authors states:

"The failure to detect association with AHR in the phase I genotyping study likely reflects low power from the very small sample suitable for AHR testing, as well as the wide spacing of the markers. These comparisons require an important caveat, namely that none of the association results reported here meet unequivocal thresholds for statistical significance; therefore it is not possible to state, based on this data, how the tests perform in locating a definitive gene predisposition locus for BP-I. Further evaluation of these chromosomal regions

with larger samples and additional markers will be required to definitely prove whether BP-I predisposition genes are located at these sites on chromosome 18 and to gain a more clear assessment of the power of the AHR and LD-T approaches for gene mapping of complex traits in population isolates."

In the declaration of Alison McInnes the findings of a study analyzing the SAVA5-ga203 interval are presented. The declaration states that 4 new microsatellite markers and 26 new polymorphisms, together with 4 previously identified markers were analyzed, using the methodology outlined in the specification, for their association with BP. The declaration states that it was determined that 5 of these markers (PH84, PH205, PH202, PH208 and TS30) are associated with BP. The declaration and brief assert that these findings support the fact that the specification provides sufficient guidance to enable the identification of additional polymorphisms associated with BP. However, while the declaration establishes that additional markers were identified that are associated with BP, the declaration does not establish that such polymorphisms were identified without undue experimentation. The fact that the methodology for identifying polymorphisms, i.e. the methods of cloning, PCR and sequencing, were routine in the art at the time the invention was made is not sufficient to establish that it is routine in the art to identify specific polymorphisms associated with BP. As discussed in the declaration, the majority of polymorphisms identified in the stated experiments were not in fact associated with BP. Thus, even after one has performed the research to identify new polymorphisms in the 500 kb interval, there is no predictable means for identifying which of these polymorphisms will be associated with BP and the polymorphisms associated with BP can only be identified through additional experimentation.

Applicants argue that the PCT publication WO 99/47535 is provided with the brief as evidence that those in the field could readily identify polymorphisms associated with BP. It is stated that this "evidence was not provided earlier, as it was believed that the arguments provided in the various amendments, as well as the Declaration of Alison McInnes, as discussed above, provided ample evidence of enablement." However, the WO publication has been reviewed but does not support Applicants contention that additional polymorphisms can be identified without undue experimentation. WO 99/47535 sets forth the extensive experimentation that was required to identify the HKNG1 gene. The present specification does not provide the specific guidance to lead one of skill in the art to the HKNG1 gene, or to the specific mutation within this gene that was found to be associated with BP. Additionally, WO 99/47535 (see pages 4-5) highlights the unpredictability in the art in identifying a specific loci associated with BP disorder (referred to therein as "BAD"), stating that:

"Mapping genes for common diseases believed to be caused by multiple genes, such as BAD, may be complicated by the typically imprecise definition of phenotypes, by etiological heterogeneity, and by uncertainty about the mode of transmission of the disease trait. With neuropsychiatric disorders there is even greater ambiguity in distinguishing individuals who carry an affected genotype from those that are genetically unaffected...Also, with complex traits such as neuropsychiatric disorders, it is difficult to genetically map the trait-causing genes because: (1) neuropsychiatric disorder phenotypes do not exhibit classic Mendelian recessive or dominant inheritance patterns attributable to a single locus, (2) there may be incomplete penetrance, i.e., individuals who do not inherit a predisposing allele may not manifest disease; (3) a phenocopy phenomenon may occur, i.e., individuals who do not inherit a predisposing allele may nevertheless develop disease due to environmental or random causes; (4) genetic heterogeneity may exist, in which case mutations in any one of several genes may result in identical phenotypes."

Applicants further traverse the rejection on the grounds that the cited prior art does not support a conclusion of non-enablement of the instant claims. It is argued that the present invention is based on studies that differed from previous studies in that the cited art teaches methods which utilize pedigree studies but not population-based studies. This argument is not convincing because the prior art was cited to show the general unpredictability in the field. While Applicants argue that they have utilized methods which are distinct from those in the cited art, Applicants have not established that the presently disclosed methods would enable one of skill in the art to identify additional polymorphisms without undue experimentation. Applicants further argue that McInnes discusses the unpredictability of identifying a gene associated with BP, but that the present claims are not directed to genes associated with bipolar mood disorder. However, as written, the claims encompass detecting any polymorphism associated with BP, including polymorphisms in a gene. In fact, Applicants have pointed to the WO 99/47535 document as providing evidence to support their contention that additional polymorphisms can be readily identified. However, the WO 99/47535 polymorphism was identified only because the gene containing this polymorphism was first delineated and characterized. Additionally, the methodology set forth in the specification (beginning at page 31) involves first identifying candidate cDNAs, sequencing and comparing these cDNAs to sequences in nucleic acid databases, identifying a gene or genes which may constitute the bipolar susceptibility gene, analyzing these genes for the presence of a polymorphism, and then determining whether any of the identified polymorphisms is associated with BP.

Lastly, it is again pointed out that claims are directed to a research project. The claims require performing method steps in which a polymorphism is discovered by either typing blood

relatives of an individual for the presence of a polymorphism and then determining whether any of these polymorphisms are associated with a phenotypic diagnosis of BP or by analyzing DNA from an individual for the presence of a polymorphism and then determining the frequency of the polymorphism on disease chromosomes and non-disease chromosomes, wherein over representation of a polymorphism indicates that the polymorphism is associated with a form of bipolar mood disorder. The specification has not provided sufficient guidance to enable one of skill in the art to practice such methods of identifying novel polymorphisms without undue experimentation.

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-12 and 25-27 are rejected under 35 U.S.C. 102(a) as being anticipated by Stine (American Journal of Human Genetics (December 1995) 57: 1384-1394; reference "D48" from the IDS filed May 27, 1999).

Stine teaches methods for detecting microsatellite polymorphisms associated with BP and methods for defining the locus on chromosome 18 that is associated with BP. In order to identify polymorphic markers for BP, Stine genotyped individuals having BP and control samples for polymorphic markers on chromosome 18p and 18q and identified polymorphic markers which are more prevalent in individuals having BP (i.e., disease chromosomes) as compared to control samples (i.e., non-disease chromosomes; see pages 1385-1386). In particular, Stine teaches methods of identifying individuals having BP wherein said methods comprise analyzing genomic

DNA for the presence of allelic variants of the marker D18S59 that are associated with BP (page 1385). The sample consisted of 243 genotyped individuals from 28 pedigrees (page 1385). The individuals genotyped were of undefined ancestry. However, in the absence of evidence to the contrary, the population genotyped is considered to be inclusive of individuals having some level of Spanish or Amerindian ancestry. Stine (see abstract) concludes that "(t)he evidence for linkage to loci on both 18p and 18q was strongest in the 11 paternal pedigrees, i.e., those in which the father or the father's sibs is affected...Our results provide further support for linkage of BPAD to chromosome 18 and the first molecular evidence for a parent-of-origin effect operating in this disorder." It is noted that the D18S59 polymorphic marker lies between (and inclusive of) the markers of SAVA5 to ga203, D18S1140 to ga203, SAVA5 to W3422, D18S11 to W3422, D16S1140 to at201, D18S1140 to ta201 and D18S59 to ta201 and the D18S59 allelic variant is considered to be a polymorphism. Furthermore, with respect to claims 1-8, 10-12, 25 and 26, the recitations of "method of detecting an increased susceptibility to bipolar mood disorder (BP)" (claims 1-8, 25 and 26), "method of genetically diagnosing bipolar mood disorder" (claims10 and 12) and "method of confirming a phenotypic diagnosis of bipolar mood disorder" (claim 11) are considered to be statements of purpose and intended result. These recitations do not result in a manipulative difference in the method steps when compared to the prior art disclosure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703)-308-1119. Papers related to this application may be faxed to Group 1634 via the PTO Fax Center using the fax number (703)-872-9306 or (703)-872-9307 (after final).

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.
Carla Myers

March 6, 2003

CARLA J. MYERS
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